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A Gutsy Way to Grow: Intestinal Stem Cells as Nutrient Sensors

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Adult tissues can rapidly and reversibly change size to adapt to environmental and behavioral influences. In this issue, O'Brien et al. (2011) demonstrate that fly intestinal stem cells alter their division patterns in response to food availability to drive organ growth.

Although adult tissues are usually regarded as homeostatic, some organs, such as muscle, liver, and intestine, have an adaptive potential to grow or shrink by functional demand (Piersma and Lindström, 1997). One well-documented example is the change in size and metabolism of the gut in response to food intake. However, the mechanism(s) by which the gut adapts its size in response to dietary load remain elusive. Now, David Bilder and colleagues (O'Brien et al., 2011) report that intestinal stem cells (ISCs) are key players in directing such a response in the fly midgut.

Like the mammalian small intestine, the *Drosophila* posterior midgut contains ISCs that homeostatically maintain organ size by generating new cells to replace tissue lost to regular turnover or injury (reviewed in Losick et al., 2011). ISCs both self-renew to maintain the stem cell population and differentiate into enteroblasts that undergo terminal differentiation into either absorptive enterocytes or secretory enteroendocrine cells every 1–2 weeks. Previous work has shown that ISC numbers remain stable under homeostatic conditions through a mechanism involving asymmetric cell divisions (Losick et al., 2011). O'Brien et al. here demonstrate that this type of classic stem cell behavior changes dramatically when the fly begins feeding after emerging from the pupal case.

Intrigued by the observation that total cell number in a progenitor-rich area of the *Drosophila* posterior midgut increased by an outstanding 300% during the first 4 days of feeding, the investigators reasoned that nutrient uptake may induce gut expansion through stem cell activation. Indeed, the authors discovered that ISCs and enteroblasts had expanded up to 3-fold upon feeding, indicating that increased stem cell division was the direct source of feeding-induced growth, consistent with a previous report (McLeod et al., 2010). The authors further hypothesized, based on mathematical calculations, that stem cells may be undergoing different division dynamics during the feeding period to generate the massive increase in cell number.

To measure the rate of symmetric versus asymmetric stem cell divisions, the authors used an elegant genetic marking system, twin-spot MARCM, to permanently label dividing stem cells with different colors. Remarkably, O'Brien et al. noticed that ISCs can switch between asymmetric and symmetric modes, depending on nutrient availability, with fed guts exhibiting a higher ratio of symmetric-to-asymmetric stem cell divisions than fasted guts. Importantly, these ratios were normalized again when fed guts reached homeostasis. Thus, the predominance of symmetric division fates appeared to be one of the main mechanisms for increasing cell number and adaptive growth during this new adult feeding period (Figure 1). Though feeding-induced organ growth is conserved in later-stage adults, it remains unclear whether this also entails a switch from asymmetric to symmetric stem cell divisions. Of note, the authors also show that apoptosis of excess cells is a mechanism to shrink organ size in starved older adults to compensate for the lack of nutrients. Another interesting observation of the presented study is that, despite an increase in absolute stem cell numbers in fed guts, the relative

fraction of stem cells per total gut cells remained constant throughout the feeding period, raising questions about the mechanisms that maintain stem cell proportions in tissues. A better understanding of this process may shed light on situations in which tissues undergo aberrant growth, including in cancer.

O'Brien et al. next examined possible signals that may communicate nutrient availability to ISCs upon feeding. Specifically, the authors focused on the insulin pathway, whose role in nutrient sensing and growth control is well established and broadly conserved. The authors noticed that only a single insulin peptide, dILP3, was upregulated upon feeding in nearby midgut visceral muscle, an area enriched for stem cell regulatory factors such as *Wingless* (Losick et al., 2011). Accordingly, the insulin receptor protein was expressed in stem cells. To assign functionality to this observation, O'Brien and colleagues performed knockdown and overexpression studies in ISCs and muscle cells, which demonstrated that dILP3 signaling is both required and sufficient for feeding-induced ISC activation. Intriguingly, insulin-related peptides are also expressed in smooth muscle cells of the mouse small intestine (Pucilowska et al., 2000) and increase in expression during adaptation (Winesett et al., 1995), raising the possibility that insulin signaling may also regulate stem cell activity in mammals through a similar muscle-intestine interaction.

Systemic insulin signaling has been previously shown to regulate the proliferation of fly intestinal and germline stem cells in response to nutrient availability or injury (reviewed in Jasper and Jones, 2010). O'Brien et al. propose that local insulin production by muscle cells synergizes with systemic insulin signaling to fine-tune stem cell activity during adaptive growth. Notably, control of stem cell activity by spatially discrete insulin production has a precedent in the developing fly central nervous system, in which quiescent neuroblasts are activated by an increase in local dILP6 produced from neighboring glial cells (Chell and Brand, 2010; Sousa-Nunes et al., 2011). Local insulin release from glial cells is regulated by an unidentified factor from the fat body, which is the fly counterpart of liver and adipose tissue in mammals and is responsible for sensing nutrient availability by TOR signaling-mediated amino acid sensing. Based on these studies, it is conceivable that the fat body may also trigger local insulin activity in visceral muscle cells, thus generating an amplification of ISCs and, consequently, organ growth. It should be possible to test this hypothesis by blocking signaling from the fat body, as was done in the neuroblast experiments (Sousa-Nunes et al., 2011).

The results of this study provide an interesting paradigm for adaptive growth in response to nutrient availability, in which stem cells respond rapidly to local changes in insulin levels to coordinate tissue remodeling. A key question that emerges from this work is how symmetric-to-asymmetric ISC division ratios are modulated upon feeding. One possibility is that ISCs are intrinsically equivalent, and feeding/changes in insulin signaling somehow bias their homeostatic division pattern from predominantly asymmetric to symmetric. This may involve a mechanism of stochastic competition among ISCs, creating a pattern of "neutral drift" akin to the mouse small intestine (reviewed in Barker et al., 2010). Alternatively, stem cells may be heterogeneous with some stem cells primarily maintaining homeostatic growth and others predominantly regulating adaptive growth. The recent description of multipotent intestinal and gastric stem cells in mouse with apparently distinct localizations, turnover rates, and responsiveness to stress (reviewed in Barker et al., 2010) may point to the existence of functionally different stem cells in mammals. Further studies are certainly warranted to resolve these fundamental questions and to elucidate conserved mechanisms by which stem cell behavior is regulated in response to nutrient availability and feeding behaviors in other species including mammals. Such experiments could provide important insights into the therapeutic use of stem cells for treatment of different gastrointestinal and metabolic disorders such as diabetes.

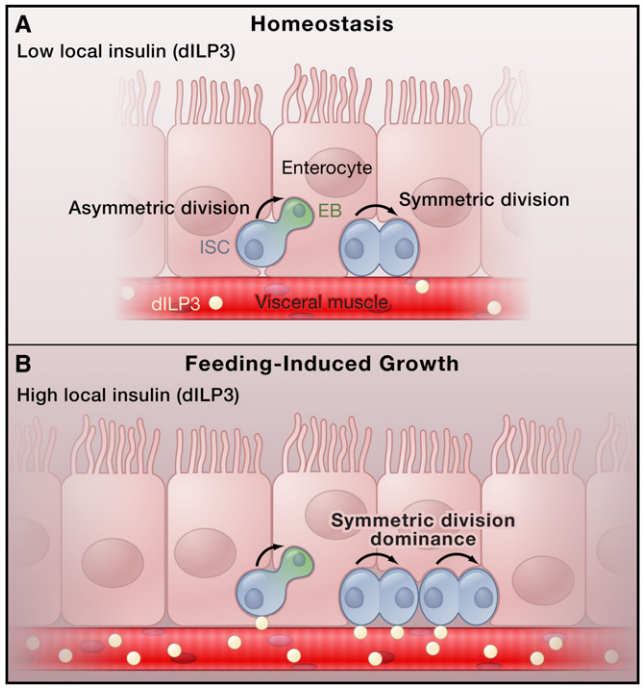

Figure 1. Intestinal Stem Cells Drive Organ Growth in Response to Food Intake

(A) Under homeostatic conditions, intestinal stem cells (ISCs) divide both asymmetrically and symmetrically to maintain the epithelium of the fly posterior midgut. ISC, intestinal stem cell; EB, enteroblast.

(B) Upon initiation of feeding, ISCs respond to an increase in local insulin signaling (dILP3) and divide more often symmetrically than asymmetrically to generate the large increase in cell number of the midgut.

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You AhR What You Eat: Linking Diet and Immunity

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The aryl hydrocarbon receptor (AhR) is responsible for the toxic effects of environmental pollutants such as dioxin, but little is known about its normal physiological functions. Li et al. (2011) now show that specific dietary compounds present in cruciferous vegetables act through the AhR to promote intestinal immune function, revealing AhR as a critical link between diet and immunity.

From childhood we learn that vegetables are good for us, and most of us eat our veggies without giving much thought to the evidence behind this accepted wisdom or to the mechanisms underlying the purported health-boosting properties of a vegetable-rich diet. In this issue of *Cell*, Li et al. (2011) uncover a link between diet and immunity, showing that specific dietary compounds found at high levels in cruciferous vegetables such as broccoli, cauliflower, and cabbage are essential for sustaining intestinal immune function. Moreover, they show that the molecular basis for this link involves the aryl hydrocarbon receptor (AhR).

The AhR is best known for mediating the toxic effects of dioxin, an environmental pollutant that is found in industrial byproducts and is a toxic contaminant of some herbicides (Fernandez-Salguero et al., 1995). AhR is part of the basic helix-loop-helix/Per-Arnt-Sim (PAS) homology superfamily, whose members play central roles in sensing environmental factors such as oxygen and light. In its inactive state, AhR resides in the cytoplasm, but upon encountering polycyclic aromatic hydrocarbons such as dioxin, it translocates to the nucleus where it heterodimerizes with the AhR nuclear translocator (Arnt). The AhR-Arnt complex activates expression of a battery of genes containing specific DNA enhancer sequences known as AhR-responsive elements (AhREs). Many AhR target genes are xenobiotic-metabolizing enzymes such as the cytochrome P450 family member Cyp1a1 (Ito et al., 2007). Early studies of mice engineered to lack AhR (*Ahr*$^{-/-}$ mice) suggested a role for AhR in liver development (Fernandez-Salguero et al., 1995). However, until recently little else was known about the physiological function of AhR or what ligands activate AhR under normal, healthy conditions.

Li et al. provide fascinating new insight into the physiological role of the AhR by showing it to be essential for normal intestinal immune function. Previous work had revealed that AhR is expressed by circulating proinflammatory T helper 17 (Th17) cells and that activation of AhR by dioxin modulates the numbers of Th17 cells in mouse models of autoimmune disease (Veldhoen et al., 2008; Quintana et al., 2008). Expanding on these prior findings, Li et al. quantified AhR expression in a broad array of immune cells isolated from various tissues. Strikingly, they found that intraepithelial lymphocytes (IELs) from intestine and skin express especially high levels of AhR. These unconventional T cells inhabit the body's epithelial barriers in large numbers, intercalating between epithelial cells and forming intimate contacts with their epithelial neighbors. IELs have a number of unusual properties relative to conventional T cells, including a high proportion of cells bearing the $\gamma\delta$ T cell receptor and a prevalence of CD8$\alpha\alpha$ coreceptors. Consistent with their positioning at epithelial surfaces, IELs defend against assaults from the environment. Essential functions include promoting epithelial repair following injury (Chen et al., 2002) and limiting epithelial cell invasion by the vast populations of